Cardiac Epi-Metabolic Signature Revealed by Integrated Omics Approach in Diabetic Patients: Rescue by Active DNA Demethylation via TET-TDG Complex Reactivation

Abstract 19033: Cardiac Epi-Metabolic Signature Revealed by Integrated Omics Approach in Diabetic Patients: Rescue by Active DNA Demethylation via TET-TDG Complex Reactivation

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Circulation. 2016;134:A19033

Abstract

Introduction & Hypothesis: Diabetes is one of the major risk factor for cardiovascular diseases. Prolonged exposure to uncontrolled hyperglycaemia in the heart induces dramatic metabolic changes that alter tissue homeostasis providing basis for the so called “metabolic memory”. Although epigenetic mechanisms have been described contributing to this process, the molecular events that establish metabolic memory remain elusive. Recent reports revealed that stable oxidation derivatives of methylated cytosines (5mC) such as 5-hydroxymethyl (5hmC) and 5-formyl (5fC) cytosines may accumulate in the heart upon age but none of these changes has been associated yet to metabolic memory or diabetes. Prior work described that human cardiac stromal cells isolated from diabetic donors (D-CSMCs) displayed stable epigenetic alterations including enrichment of 5mC. We queried here about the existence of an epi-metabolic control circuit capable of regulating DNA demethylation enzymatic machinery and the onset of metabolic memory diabetic tissues and cells.

Methods & Results: An integrated genomic, transcriptomic and metabolomic approach revealed that 5mC, 5hmC and 5fC accumulated in genomic and mitochondrial DNA from hearts of diabetic mice and in D-CMSCs. Specifically, RNA-seq indicated repression of genes associated to proliferation, transcription, DNA repair and metabolism while metabolomics provided evidence of a reduction in alpha-ketoglutaric acid (αKG) synthesis. Notably, αKG deficiency compromised ten eleven translocation (TET) and thymine DNA glycosylase (TDG) complex formation and function. Providing an exogenous source of αKG to cells, in fact, reactivated TET and TDG and reduced the genomic content of modified cytosines. To select more specific modulators a drug screening was performed to select small molecule regulators of αKG synthesis and DNA demethylation. The newly identified compound, AA6, increased the intracellular content of αKG and activated TET and TDG resulting in genomic demethylation and functional rescue of type 2 diabetic mice and human cells.

Conclusions: The epi-metabolic modulation of DNA demethylation promises novel future therapeutic strategies aimed at prevention/treatment of diabetic cardiac complications.